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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/926,001	09/17/2001	Ulf Schroder	SCHR3003/REF	6616

7590 01/27/2004

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EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	10

DATE MAILED: 01/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/926,001	SCHRODER ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

FINAL ACTION

1. This Office Action is responsive to Applicant's amendment and response filed May 13, 2002. Claims 1-10 have been cancelled. Claims 11-46 have been added.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

Rejections Withdrawn

3. In view of Applicant's amendment and response the following rejections are withdrawn:

a) The Nonstatuatory Double Patenting rejection of claims 1-10, pages 2-3, paragraph 1 of previous Office action.

b) Rejection of claim under 35 U.S.C. 112, second paragraph, page 3, paragraph 2 of previous Office action.

c) Rejection of claim 3 under 35 U.S.C. 112, second paragraph, pages 3-4, paragraph 3 of previous Office action.

d) Rejection of claim 4 under 35 U.S.C. 112, second paragraph, page 4, paragraph 4 of previous Office action.

e) Rejection of claim 5 under 35 U.S.C. 112, second paragraph, page 4, paragraph 5 of previous Office action.

f) Rejection of claim 46 under 35 U.S.C. 112, second paragraph, pages 15-16, paragraph 14 of previous Office action.

g) Rejection of claims 1-2, 7, 11, 14, 24, 26, 28-34, 36, 38 and 40-46 under 35 U.S.C. 102(b), pages 16-17 , paragraph 15 of previous Office action.

Rejections Maintained

4. The rejection of newly submitted claims 11-16, 18-27 and 29-36 under 35 U.S.C. 103(a) as unpatentable over Youmans et al in view of Schroder is maintained for the reasons set forth on pages 4-6, paragraph 6 of the previous Office Action.

The rejection was on the grounds Youmans et al teach a tuberculosis vaccine comprising killed *Mycobacterium tuberculosis* which were killed by heat or chemicals (page 108). Youmans et al teach that the *Mycobacterium tuberculosis* were contained in phosphate buffer solution (page 109). Youmans et al teach that mice were administered the killed vaccine both with and without an adjuvant (pages 111-112).

Youmans et al do not teach adjuvants that comprise monoglycerides.

Schroder teaches the use of monoglycerides as adjuvants. Schroder teaches that the parenteral or mucosal administration of a pharmaceutical formulation containing monoglycerides (i.e. mono-olein/oleic acid) improves the immune response against admixed antigens/vaccines (page 4, lines 16-25). Schroder teaches that a combination between a monoglyceride and a fatty acid can stimulate the immune system to produce antibodies and induce protective immunity (page 7, lines 6-9). Limitations such as "mucosal administration is being view as a limitation of intended use. However, it is well known in the art that lipid preparations that are used as adjuvants are not restricted to one mode of administration and can be used in many routes of administration including mucosal. Limitations such as packaging the vaccine as an aersol, spray or nose-drop package is being viewed as a limitation of design choice.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to add the monoglyceride preparation as taught by Schroder to the *Mycobacterium tuberculosis* of Youmans et al because Schroder teaches that a combination between a monoglyceride and a fatty acid can stimulate the immune system to produce antibodies and induce protective immunity (page 7, lines 6-9). It would have been expected barring evidence to the contrary, that the addition of monoglycerides to *Mycobacterium tuberculosis* vaccines would provide enhancement of immunological responses after administration of monoglycerides and/or fatty acids together with antigens and the use of monoglycerides in vaccines are stable, cheaper and easy to formulate.

Applicant urges that there must be some suggestion or motivation either in the references themselves or in the knowledge generally available to one of ordinary skill in

the art to modify the reference or to combine the reference teachings. Applicant urges that there must be a reasonable expectation of success and the art must teach or suggest all the claim limitations. Applicant urges that Schroder suggests an adjuvant for use in a vaccine formulation but does not suggest a TB vaccine. Applicant urges that Youmans et al teach a comparison between tuberculosis vaccine comprising either viable attenuated cells or heat-killed or chemically killed cells. Applicant urges that Youmans et al do not indicate that a TB vaccine comprising inactivated *Mycobacterium tuberculosis* would be effective. Applicant urges that it is impermissible to engage in hindsight reconstruction of the claimed invention using the Applicant's structure as a template and selecting elements from references to fill the gaps.

Applicant's arguments filed May 13, 2002 have been fully considered but they are not persuasive. It is the Examiner's position that applicant argues the references individually without clearly addressing the combination of teachings. It is the combination of all of the cited and relied upon references which make up the state of the art with respect to the claimed invention. The claims are drawn to a tuberculosis vaccine composition comprising an adjuvant one of more substances selected from the group consisting of: a) monoglyceride preparations, b) a fatty acid and c) as a immunizing component, inactivated *Mycobacterium tuberculosis* bacteria and an aerosol, spray or nose package comprising the TB vaccine. Youmans et al teach a tuberculosis vaccine comprising killed *Mycobacterium tuberculosis.* Youmans et al do not teach adjuvants that comprise monoglycerides. However, Schroder teaches the use of monoglycerides as adjuvants. Although "routes of administration" (i.e. nasal,

pulmonary, oral or vaginal) are limitations of intended use, Schroder teaches that the parenteral or mucosal administration of a pharmaceutical formulation containing monoglycerides (i.e. mono-olein/oleic acid) improves the immune response against admixed antigens/vaccines (page 4, lines 16-25). It would be obvious to add the adjuvant comprising monoglyceride preparations and fatty acids as taught by Schroder to the tuberculosis vaccine comprising killed *Mycobacterium tuberculosis* of Youmans et al because Schroder teaches that a combination between a monoglyceride and a fatty acid can stimulate the immune system to produce antibodies and induce protective immunity. It should be remembered that claim limitations as "an aerosol, spray or nose package" are being viewed as limitations of design choice.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the

applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). It is the Examiner's position that there is nothing on the record to teach or suggest that the combination of references do not teach the claimed invention.

5. The rejection of newly submitted claims 38-45 under 35 U.S.C. 103(a) as unpatentable over Youmans et al in view of Schroder is maintained for the reasons set forth on pages 6-7 paragraph 7 of the previous Office Action.

The rejection was on the grounds that Youmans et al teach a method of vaccinating mice comprising administering killed *Mycobacterium tuberculosis* with and without Freund's adjuvant (pages 111-112). Youmans et al teach that administration of the tuberculosis vaccine did indeed provoke immune response (page 110).

Youmans et al do no teach the use of monoglycerides as adjuvants.

Schroder teaches a method of vaccinating mice comprising a diphtheria antigen and a monoglyceride preparation (page 9, example 4). Schroder teaches that both IgG as well as protective antibody titers were at the same level as compared to the control groups which received a composition of diptheria toxoid and alum. Schroder also teaches that the high IgG titers always were accompanied by high neutralization titers indicating that the formulations do no destroy the antigenic sites that are important for protective immunity (page 9, Example 4).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to add the to monoglyceride preparation of Schroder to the *Mycobacterium tuberculosis* vaccine composition used in the method of vaccinating a mammal as taught by Youmans et al because Schroder teaches that the parenteral or mucosal administration of a pharmaceutical formulation containing monoglycerides (i.e. mono-olein/oleic acid) improves the immune response against admixed antigens/vaccines (page 4, lines 16-25). It would have been expected barring evidence to the contrary, that the addition of monoglycerides to *Mycobacterium tuberculosis* vaccines would provide enhanced immunogenicity of antigens and that formulations are stable, inexpensive and easy to formulate.

Applicant urges that the claims as amended includes administration of a vaccine composition comprising the L3 adjuvant and inactivated mycobacterium. Applicant

urges that Youmans et al do not teach the use of adjuvants as beneficial therefore the method of using inactivated *M. tuberculosis* cell provides very poor results. Applicant urges that the combination of references would not provide for an effective method of vaccinating an animal.

Applicant's arguments filed May 13, 2002 have been fully considered but they are not persuasive. It is the Examiner's position that applicant argues the references individually without clearly addressing the combination of teachings. It is the combination of all of the cited and relied upon references, which make up the state of the art with respect to the claimed invention. The claims are drawn to a method of vaccinating a mammal against TB which comprises mucosal administration to the mammal of a protection-inducing amount of a tuberculosis vaccine composition comprising an adjuvant one of more substances selected from the group consisting of: a) monoglyceride preparations, b) a fatty acid and c) as a immunizing component, inactivated *Mycobacterium tuberculosis* bacteria. Youmans et al a method of vaccinating mice comprising administering killed *Mycobacterium tuberculosis* with and without Freund's adjuvant (pages 111-112). Youmans et al do not teach the use of monoglycerides as adjuvants. However, Schroder teaches the use of monoglycerides as adjuvants. Although "routes of administration" (i.e. nasal, pulmonary, oral or vaginal) are limitations of intended use, Schroder teaches that the parenteral or mucosal administration of a pharmaceutical formulation containing monoglycerides (i.e. mono-olein/oleic acid) improves the immune response against admixed antigens/vaccines (page 4, lines 16-25). It would be obvious to add the adjuvant comprising

monoglyceride preparations and fatty acids as taught by Schroder to the tuberculosis vaccine comprising killed *Mycobacterium tuberculosis* of Youmans et al because Schroder teaches that a combination between a monoglyceride and a fatty acid can stimulate the immune system to produce antibodies and induce protective immunity. In regards to Applicant's arguments concerning that the method would not be an effective method of vaccinating mammals, it should be noted that Youmans et al teach that administration of the tuberculosis vaccine did indeed provoke immune response and Schroder teaches that the parenteral or mucosal administration of a pharmaceutical formulation containing monoglycerides (i.e. mono-olein/oleic acid) improves the immune response against admixed antigens/vaccines. It is the Examiner's position that there is nothing on the record to teach or suggest that the combination of references do not teach the claimed invention.

New Grounds of Rejection Necessitated by Amendment

Claim Objections

6. The claims are objected to for the following informalities: the names of microorganisms should be underlined or italicized. Correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 11-37 are rejected under 35 U.S.C. 103(a) as unpatentable over Youmans et al *(Journal of Bacteriology, January 1969, p. 107-113)* in view of Schroder *(WO 97/47320, published December 1997)* and further in view of Van Nest et al *(U. S. Patent No. 6,451,325, published September 17, 1992).*

Claims 11-37 are drawn to a tuberculosis vaccine composition comprising as adjuvant one or more substances selected from monoglyceride preparations having 80% monoglyceride content.

Youmans et al teach a tuberculosis vaccine comprising killed *Mycobacterium tuberculosis* which were killed by heat or chemicals (page 108). Youmans et al teach that the *Mycobacterium tuberculosis* were contained in phosphate buffer solution (page 109). Youmans et al teach that mice were administered the killed vaccine both with and without an adjuvant (pages 111-112).

Youmans et al do not teach adjuvants that comprise monoglycerides.

Schroder teaches the use of monoglycerides as adjuvants. Schroder teaches that the parenteral or mucosal administration of a pharmaceutical formulation containing monoglycerides (i.e. mono-olein/oleic acid) improves the immune response against admixed antigens/vaccines (page 4, lines 16-25). Schroder teaches that a combination between a monoglyceride and a fatty acid can stimulate the immune system to produce antibodies and induce protective immunity (page 7, lines 6-9). Limitations such as "mucosal administration is being view as a limitation of intended use. However, it is well known in the art that lipid preparations that are used as adjuvants are not restricted to one mode of administration and can be used in many routes of administration including mucosal. Limitations such as packaging the vaccine as an aersol, spray or nose-drop package is being viewed as a limitation of design choice.

Youmans et al and Schroder do not teach soybean oil.

Van Nest et al teach the use of any metabolizable oil (for example, soybean oil) in an adjuvant formulation (column 3, lines 62-67 – column 4, lines 1-11). Van Nest et al teach that the oil component of the adjuvant can be present in an amount from 0.5% to 20% by volume (column 4, lines 49-53). Van Nest et al teach that metabolizable oils such as soybean oil are used in vaccines because unmetabolizable oils when administered may cause abscesses, granulomas or even carcinomas and meat of birds and animals vaccinated with oil other than metabolizable oils may be unacceptable for human consumption due to the deleterious effect that unmetabolizable oils have on the consumer (column 3, lines 62-67 and column 4, lines 1-3).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to add the monoglyceride preparation as taught by Schroder to the *Mycobacterium tuberculosis* of Youmans et al and the soybean oil as taught by Van Nest et al because Schroder teaches that a combination between a monoglyceride and a fatty acid can stimulate the immune system to produce antibodies and induce protective immunity (page 7, lines 6-9) and Van Nest et al teach that metabolizable oils such as soybean oil are used in vaccines because unmetabolizable oils when administered may cause abscesses, granulomas or even carcinomas and meat of birds and animals vaccinated with oil other than metabolizable oils may be unacceptable for human consumption due to the deleterious effect that unmetabolizable oils have on the consumer (column 3, lines 62-67 and column 4, lines 1-3). It would have been expected barring evidence to the contrary, that the addition of an adjuvant comprising monoglycerides and soybean oil to *Mycobacterium tuberculosis* vaccines would provide enhancement of immunological responses to the *Mycobacterium tuberculosis* antigen.

8. Claims 38-46 are rejected under 35 U.S.C. 103(a) as unpatentable over Youmans et al *(Journal of Bacteriology, January 1969, p. 107-113)* in view of Schroder *(WO 97/47320, published December 1997)* and further in view of Van Nest et al *(U. S. Patent No. 6,451,325, published September 17, 1992).*

Claims 38-46 are drawn to a method of vaccinating a mammal against Tuberculosis which comprises mucosal administration to the mammal of a protection-inducing amount of a tuberculosis vaccine composition.

Youmans et al teach a method of vaccinating mice comprising administering killed *Mycobacterium tuberculosis* with and without Freund's adjuvant (pages 111-112). Youmans et al teach that administration of the tuberculosis vaccine did indeed provoke immune response (page 110).

Youmans et al do no teach the use of monoglycerides as adjuvants.

Schroder teaches a method of vaccinating mice comprising a diphtheria antigen and a monoglyceride preparation (page 9, example 4). Schroder teaches that both IgG as well as protective antibody titers were at the same level as compared to the control groups which received a composition of diptheria toxoid and alum. Schroder also teaches that the high IgG titers always were accompanied by high neutralization titers indicating that the formulations do no destroy the antigenic sites that are important for protective immunity (page 9, Example 4).

Youmans et al and Schroder do not teach soybean oil.

Van Nest et al teach the use of any metabolizable oil (for example, soybean oil) in an adjuvant formulation (column 3, lines 62-67 – column 4, lines 1-11). Van Nest et

al teach that the oil component of the adjuvant can be present in an amount from 0.5% to 20% by volume (column 4, lines 49-53). Van Nest et al teach that metabolizable oils such as soybean oil are used in vaccines because unmetabolizable oils when administered may cause abscesses, granulomas or even carcinomas and meat of birds and animals vaccinated with oil other than metabolizable oils may be unacceptable for human consumption due to the deleterious effect that unmetabolizable oils have on the consumer (column 3, lines 62-67 and column 4, lines 1-3).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to add the monoglyceride preparation as taught by Schroder to the *Mycobacterium tuberculosis* of Youmans et al and the soybean oil as taught by Van Nest et al use in a method of vaccinating a mammal because Schroder teaches that a combination between a monoglyceride and a fatty acid can stimulate the immune system to produce antibodies and induce protective immunity (page 7, lines 6-9) and Van Nest et al teach that metabolizable oils such as soybean oil are used in vaccines because unmetabolizable oils when administered may cause abscesses, granulomas or even carcinomas and meat of birds and animals vaccinated with oil other than metabolizable oils may be unacceptable for human consumption due to the deleterious effect that unmetabolizable oils have on the consumer (column 3, lines 62-67 and column 4, lines 1-3). It would have been expected barring evidence to the contrary, that the addition of an adjuvant comprising monoglycerides and soybean oil to *Mycobacterium tuberculosis* vaccines would provide enhancement of immunological responses to the *Mycobacterium tuberculosis* antigen.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308–3909.

Vanessa L. Ford
Biotechnology Patent Examiner
January 21, 2004

JAMES O. WILSON
SUPERVISORY PATENT EXAMINER
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